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Stephen M. Purcell DO

Lehigh Valley Health Network, Stephen.Purcell@lvhn.org

Tatyana Groysman DO

Lehigh Valley Health Network, Tatyana.Groysman@lvhn.org

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Plexiform Neurofibroma Associated with NF1

Stephen M. Purcell, DO and Tatyana Groysman, DO, Lehigh Valley Health Network, Allentown, Pennsylvania

Patient: D.G., a 55 year-old Caucasian male.



Figure 1: Overhanging from the posterior neck is a tender mass with overgrowth of epidermal and subcutaneous tissues. Also multiple flesh-toned, pink and tan polypoid, soft, rubbery nodules varying in size scattered throughout back.

Figure 2: Side view of the overhanging bag-like mass.

Figure 3: Another diffuse, thick and irregular tumor is noted on the right shoulder.

History of Present Illness: The patient presented to the dermatology clinic complaining of a mass extending from the back of his neck. Associated symptoms included headaches, pain upon lying down and sleeping, as well as inability to keep proper hygiene of the area involved. The physical disfigurement significantly affected the patient's quality of life. He reported a prior surgical excision at the site in childhood. Overtime the lesion recurred, enlarging in size gradually in a span of 15-20 years. Multiple other neurofibromas were excised in the past, particularly one on his left flank and his right shoulder. Unfortunately the patient died of cardio-pulmonary causes in late February.

Medical History/Surgical History: NF1, left Horner syndrome, COPD, sleep apnea, GERD, DM II, adenocarcinoma of the colon, C2-C4 laminectomy with fusion using left ilial bone graft as a child, left inguinal herniorrhaphy, multiple neurofibromas excised as per patient

Family History: NF1 in his father, brother, sister, aunts and uncles. He has 2 sisters who are not affected. Work up of his two daughters is in progress.

Medications: Gabapentin, mirtazapine, diclofenac, glucophage, omeprazole, montelukast, ipratropium inhaler, salbutamol inhaler, fluticasone propionate nasal spray

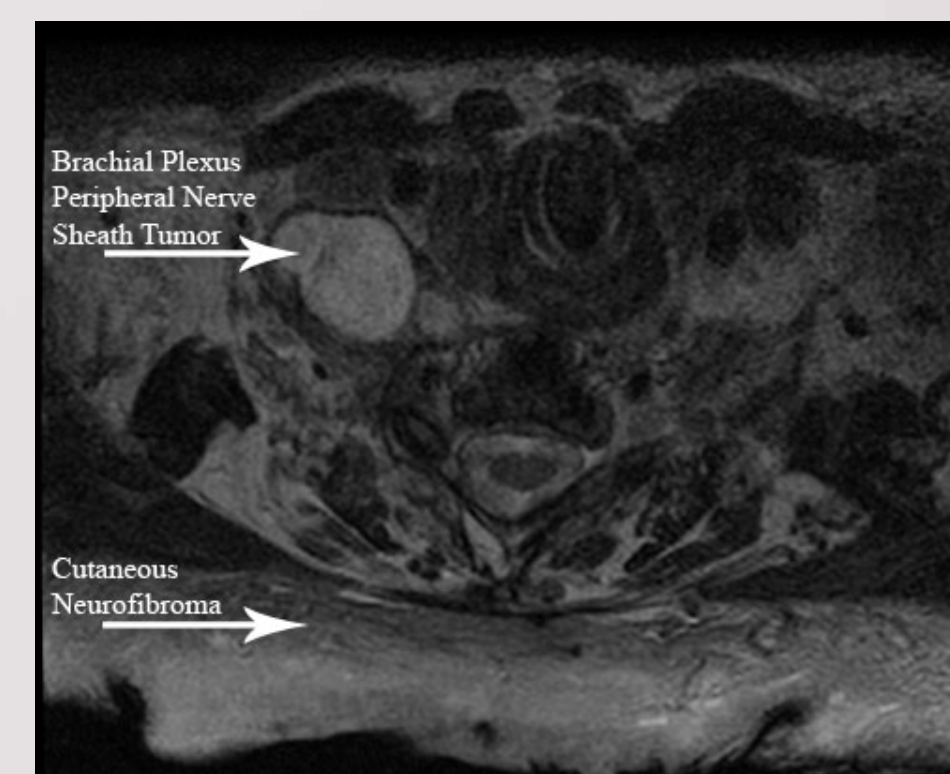
Previous Treatments: Surgical excisions

Physical Examination: Overhanging from the posterior neck a tender mass with overgrowth of epidermal and subcutaneous tissue associated with a wrinkled and "peau d'orange" texture. Another diffuse, thick and irregular tumor is noted on the right shoulder. Multiple flesh-toned, pink and tan polypoid, soft, rubbery nodules varying in size scattered throughout the trunk and extremities. Axillary freckling is present.

Studies: Cervical spine MRI, April 2007: "7.1x2.3x2.8 cm plexiform neurofibroma arising from the roots and trunks of the right brachial plexus. Right C2-C3 through C6-C7 neural foraminal neurofibromas or schwannomas, the largest of which measures approximately 1.7 cm at C4-C5. Small nerve sheath tumor of the adipose tissues inferior to the left occipital bone". Cervical spine MRI in September 2010 showed "no interval change involving the right brachial plexus neurofibroma but did reveal enlargement of exiting nerve roots bilaterally, more on the right side without a discrete mass."

Reason for Presentation: Interest

Discussion: Plexiform neurofibroma (PN) is a benign peripheral nerve sheath tumor, considered to be pathognomonic of neurofibromatosis type 1 (NF1). It is seen in about 15-30% of individuals with NF1, typically presenting at birth or becoming physically apparent within the first 2-5 years of life. PN clinically features a diffuse large, bag-like mass, often with overlying hyperpigmentation or hypertrichosis. The tumors can be severely disfiguring and locally invasive, most commonly involving the trigeminal or upper cervical nerves.



Axial T2-weighted cervical spine MRI (4-24-2007)

Histopathologically, PNs are similar to discrete neurofibromas: a myxomatous, hypocellular background with spindle cells, mast cells, fibroblasts and vascular components arranged in closely packed multiple fascicles. The tumor is intra-neural and each part of the plexus is confined by a thickened perineurium.

The natural progression of PN is poorly understood. Certain lesions remain quiescent for a long time, whereas others may grow aggressively, especially during childhood and adolescence. Rarely, rapid growth or pain can be suggestive of malignant transformation. With a lifetime risk of 8-13%, malignant peripheral nerve sheath tumors (MPNSTs) are not uncommon in NF1 and are one of the leading causes of premature death. They carry a poor prognosis with a 5-year survival of only 21-41%.

There is increasing evidence that mutations in genes other than the NF1 gene contribute to the development of malignancies. Studies have shown that inactivation of the p53 tumor suppressor gene, upregulation of the CD44 adhesion molecule and decreased or lost PTEN expression accompanies MPNST formation.

The management of patients with PN is not well defined and is aimed mostly at controlling symptoms. Surgical approach is difficult, as it produces poor results with a high rate of re-growth and potential risk for long-term neurologic sequelae. Routine MRI scans may be of value in monitoring patients with rapidly growing tumors.

A novel therapeutic option has emerged as a result of recent research in PN pathogenesis. A mouse model study concluded that tumor formation is driven by NF1 heterozygosity in marrow, particularly the mast cells expressing high-functioning c-kit receptors. Genetic inhibition of c-kit protects against tumorigenic potential, further confirming these findings. As such, imatinib mesylate (Gleevec), a potent inhibitor of c-kit receptor tyrosine kinase, successfully reduced existing PN volume in a mouse model. A case report of a critically ill three-year-old girl with a PN compressing her airway had a 75% volume reduction of her tumor with imatinib administration. Imatinib for PN management is now a phase II clinical trial in its final stages.

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